

Case Report:

Extra-pulmonary tuberculosis infection in the dialysis patients with end stage renal diseases: case reports and literature review

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Abstract: The diagnosis of extra-pulmonary tuberculosis (TB) seems relatively difficult due to the absence of specific symptoms and signs in patients on peritoneal dialysis or hemodialysis. We report four cases of extra-pulmonary tuberculosis on dialysis, with two cases on peritoneal dialysis and two cases on hemodialysis. The presentations, therapy, and outcomes of TB infection in these patients were reviewed. Otherwise, the English literature published in the PubMed database associating extra-pulmonary tuberculosis on dialysis over the last three decades is reviewed. A total of 61 studies containing 70 cases were included. The most common primary disease was diabetic nephropathy (22.86%, 16/70). The peritoneum (31.42%, 22/70), bone (21.42%, 15/70), and lymph node (20%, 14/70) were the most frequently infected. Single organ infection was common (90%, 63/70). Fever (58.57%, 41/70), pain (35.71%, 25/70), and enlarged lymph node (20%, 14/70) were the most common symptoms. Biopsy (67.14%, 47/70) and culture (40%, 28/70) provided most reliable methods for clear diagnosis of tuberculosis. The combined treatment of isoniazid, rifampicin, pyrazinamide, and ethambutol (44.29%, 31/70) was the most common therapy. The majority of patients improved (82.86%, 58/70); however, 12 cases got worse (17.14%), with 10 of them dying (14.29%). Physicians should be aware of the non-specific symptoms and location of infection, and consider tuberculosis in their differential diagnoses in dialysis patients presenting with symptoms such as fever, pain, and weight loss.

Key words: Extra-pulmonary tuberculosis, End stage renal disease, Dialysis

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1 Introduction

The incidence of tuberculosis (TB) has been increasing worldwide. One in every three people in the world is infected with the tubercle bacillus bacteria (Hung *et al.*, 2004). Many risk factors are associated with TB, such as human immunodeficiency virus (HIV) infections, transplant recipients, substance abuse, renal insufficiency, malignancy, and low socio-economic status (Lee *et al.*, 2009; Li *et al.*, 2011). Increased TB incidence is also seen in dialysis patients (Pradhan *et al.*, 1974; Ates *et al.*, 2010). Because of cellular immunity defects, patients with

end-stage renal disease (ESRD) are at increased risk of developing TB (El-Shahawy *et al.*, 1994; Lui *et al.*, 2001; 2007; Kuno *et al.*, 2010). The incidence of TB in dialysis patients is 6–16 times higher than that in the general population (Kuo *et al.*, 2001; Verettas *et al.*, 2006; Borrajo *et al.*, 2009). However, the clinical manifestations of TB in patients on dialysis are quite non-specific (Oner-Eyuboglu *et al.*, 1999; Fukasawa *et al.*, 2001; Ko *et al.*, 2004), making a timely diagnosis difficult. Moreover, the infected locations are often extra-pulmonary (Tarng *et al.*, 1998; Nakamura *et al.*, 2009). Here we report four cases of extra-pulmonary TB in ESRD patients on dialysis. Three cases presented with low-grade fever, the other presented with weight loss, finally diagnosed as extra-pulmonary tuberculosis (one bone, one lymph node, and two urinary tract infections).

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2 Case Reports

Case 1: A 67-year-old female with ESRD due to chronic glomerulonephritis had been on continuous ambulatory peritoneal dialysis (CAPD) since October 2008. She complained of intermittent fever and back pain for more than 4 months. Her body temperature fluctuated between 38.0 and 39.0 °C, with no chills or night sweats. The laboratory tests showed that her hemoglobin (HGB) levels were 86 g/L, erythrocyte sedimentation rate (ESR) was 105 mm/h (normal <20 mm/h), and C-reactive protein (CRP) levels were 0.95 mg/dl (normal <0.8 mg/dl). The tuberculin skin test (TST) was strongly positive. Chest X-ray showed a proliferative lesion in the lower left lung. The computed tomography (CT) scan of the lumbar vertebrae demonstrated the destructive lesion in the fifth vertebrae. A presumptive diagnosis of lumbar vertebrae TB was made, and the empirically diagnostic anti-TB therapy of isoniazid (INH) and rifampin (RFP) was initiated. She showed significant improvements with no fever or lumbar pain after one month. The anti-TB treatment was given for 12 months, keeping the condition under control with no recurrence of fever or lumbar pain. The CT scan of lumbar vertebrae also showed no active TB focus.

Case 2: A 46-year-old male with ESRD secondary to hypertension commenced hemodialysis (HD) in January 2010. One month later, the patient developed low-grade fever. His temperature ranged from 37.0 to 37.7 °C, at nights, with no chill or night sweats. The laboratory examination showed significant increases of ESR and CRP to 100 mm/h and 1.69 mg/dl, respectively. The serum anti-TB antibody was negative. The acid-fast bacilli were detected in the urine three times. The ultrasound of the kidneys showed no signs of obstruction. Diagnosis of urinary tract TB was made and the combined anti-TB treatment of INH, RFP, pyrazinamide (PZA), and ethambutol (EMB) was given immediately. The fever vanished after two weeks of treatment. The urine was retested one month later and no acid-fast bacilli were detected. The patient received anti-TB therapy for 12 months, keeping the condition under control with no recurrence of fever.

Case 3: A 76-year-old male with ESRD due to chronic nephritis began regular HD in July 2010. The patient developed low-grade fever and no other

symptoms accompanied. The body temperature fluctuated between 37.2 and 38.5 °C. Upon admission, his laboratory tests showed that HGB 71 g/L and ESR 110 mm/h. Smear of acid-fast bacilli in the urine was positive three times, confirming the diagnosis of urinary tract TB. The ultrasound of the kidneys showed no signs of obstruction. An anti-TB therapy of INH, RFP, and EMB was administered afterwards. The fever was gone after two weeks of treatment. The urine was retested one month later and no acid-fast bacilli were found. The patient remained on anti-TB treatment for 18 months, which kept the condition under control with no recurrence of fever.

Case 4: A 48-year-old male with ESRD due to chronic nephritis started CAPD in March 2009. The patient complained of severe headache in May 2010, and reported significant weight loss in the recent months. The laboratory tests showed the levels of ESR and CRP increased to 85 mm/h and 2.8 mg/dl, respectively. The tumor-screening tests for the gastrointestinal tract and the hematological system were negative. Later, an enlarged lymph node was found in his neck and the biopsy showed typical pathologic changes of caseating granulomas. An anti-TB therapy of INH, RFP, and EMB was given. After three months, the patient developed numbness in his lower extremities, and subsequently discontinued treatment.

The clinical characteristics of the reported four cases are summarized in Table 1.

3 Review of the literature

The English literature published from Jan. 1, 1980 to Jan. 1, 2010, was searched in the PubMed database using the key words “dialysis” and “tuberculosis”. The article type was confined to case reports. The diagnosis of extra-pulmonary TB in dialysis population was the inclusion criteria, whether the patients were adult or children. A total of 61 studies containing 70 cases were included.

The clinical characteristics of the included studies are summarized in the Tables 2–4. The clinical characteristics of the different types of dialysis are summarized in the Table 5. Data were analyzed using the chi square and *t* tests. A *P*-value of less than 0.05 was considered to be statistically significant.

Two cases had a history of TB. One was

Table 1 Clinical characteristics of the reported four cases

Patient No.	Age (year)/sex	Primary disease	Dialysis/time (month)	Clinical symptom	Location of TB	Treatment/time (month)	Follow-up time (month)	Outcome
1	67/F	CGN	PD/15	Fever, back pain	Lumbar vertebrae	HR/12	18	Remission
2	46/M	HTN	HD/1	Fever	Urinary tract	HRZE/12	18	Remission
3	76/M	CN	HD/0.5	Fever	Urinary tract	HRE/18	18	Remission
4	48/M	CN	PD/2	Weight loss	Lymph node	HRE/3	18	Discontinuation of therapy for side effects

HD: hemodialysis; PD: peritoneal dialysis; CGN: chronic glomerulonephritis; HTN: hypertension; CN: chronic nephritis; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol

Table 2 Basic information of the reported cases

Variation	Value
Age (year)	51.37±17.78*
n _M :n _F	34:36 [#]
Time on dialysis (month)	35.78±38.12
Dialysis	
HD	43 (61.43%) [*]
PD	27 (38.57%)
Primary disease	
DM	16 (22.86%)
CGN	5 (7.14%)
HTN	3 (4.29%)
SLE	3 (4.29%)
CIN	3 (4.29%)
PKD	2 (2.86%)
NS	2 (2.86%)
Others	12 (17.14%)
Not reported	24 (34.29%)

HD: hemodialysis; PD: peritoneal dialysis; DM: diabetes mellitus; CGN: chronic glomerulonephritis; HTN: hypertension; SLE: systemic lupus erythematosus; CIN: chronic interstitial nephritis; PKD: polycystic kidney disease; NS: nephrotic syndrome. * Values are expressed as mean±SD or n (%); [#] n_M:n_F=number (male):number (female)

diagnosed with lymph-node TB based on a biopsy and had been on anti-TB therapy for nine months and five years before starting dialysis (Hung *et al.*, 2003). The other patient, diagnosed with pulmonary TB by chest X-ray, had been initiated on anti-TB treatment before renal transplant, but later turned to dialysis due to graft rejection (Prakash, 1999).

Although TB was found in most organs of the body, it was most frequently reported in the peritoneum, bone, and lymph node. Some relatively uncommon cases were also reported, including intestinal TB, renal TB, breast TB, and tuberculous orchitis

(Peces *et al.*, 1996; Alper *et al.*, 2004; Siu *et al.*, 2008; Yazici *et al.*, 2011).

Tuberculous peritonitis (TBP) (*n*=22) took up the largest part of extra-pulmonary TB. Abdominal pain or discomfort was the most common clinical presentation (*n*=15), followed by fever (*n*=14) and cloudy dialysate (*n*=8). The white blood cell (WBC) count of peritoneal dialysate ranged from 120 to 3 000/L. A predominance of neutrophils was more common in peritoneal dialysate (*n*=13). Four cases reported development of hypercalcemia (Lee *et al.*, 2002; Wang *et al.*, 2005; Borrajo *et al.*, 2009; Kuno *et al.*, 2010), with three cases on HD, one case on peritoneal dialysis (PD). The condition improved with normalization of hypercalcemia after the anti-TB treatment. It was concluded that hypercalcemia can be an early sign of TBP in the absence of obvious symptoms (Lee *et al.*, 2002), but hypercalcemia related to dialysis should be excluded.

Single organ infections were common, occurring in 90% of the patients (*n*=63). The remaining seven patients were infected as follows: peritoneum with lung involvement (*n*=3), lymph node with breast involvement (*n*=1), lymph node with liver involvement (*n*=1), lymph node with parathyroid gland involvement (*n*=1), and liver with joint involvement (*n*=1).

Fever, pain, and enlarged lymph nodes were the most common symptoms in the different focus of extra-pulmonary TB. The non-specific symptoms such as body weight loss, anorexia, and vomit were common. Anemia was common in the patients. HBG was reported in 35 cases (50%), with a mean value of 87.91 g/L (range from 50 to 124 g/L). The inflammation indexes, CRP and ESR, significantly increased. CRP was available in 26 cases (37.14%), with a mean

Table 3 Clinical symptom and location of the reported cases

Variation	Case number	Percentage (%)
Clinical symptoms		
Fever	41	58.57
Pain	25	35.71
Enlarged lymph node	14	20.00
Hypercalcemia	7	10.00
HPS	4	5.71
Painless mass	5	7.14
Increased CA125	2	2.86
Location of TB		
Peritoneum	22	31.42
Bone	15	21.42
Lymph node	14	20.00
Bone marrow	4	5.71
Lung	3	4.29
Spleen	3	4.29
Liver	2	2.86
Esophagus	2	2.86
Parathyroid gland	2	2.86
Brain	2	2.86
Latent	2	2.86
Others	6	8.57
Method of diagnosis		
Biopsy	47	67.14
Culture	28	40.00
Smear	21	30.00
PCR	16	22.86
PPD	17	24.29

HPS: hemophagocytic syndrome; TB: tuberculosis; PCR: polymerase chain reaction; PPD: purified protein derivative

Table 4 Treatment and outcome of the reported cases

Variation	Case number	Percentage (%)
Treatment		
HRZE	31	44.29
HRE	12	17.14
HRZ	9	12.85
Others	5	7.14
Unknown	13	18.57
Side effect		
INH	2	2.86
RFP	1	1.43
EMB	1	1.43
Outcome		
Better	58	82.86
Deteriorate	12	17.14

H, INH: isoniazid; R, RFP: rifampicin; Z: pyrazinamide; E, EMB: ethambutol

Table 5 Clinical characteristics of TB infection on different dialysis

Variation	Case number		P-value
	HD (n=43)	CAPD (n=27)	
Age (year)	54.37±17.26*	46.59±17.52*	0.038
n _M :n _F	23:20#	11:16#	0.299
Primary disease			0.403
DM	10	6	
SLE	0	3	
CGN	3	2	
CIN	3	1	
Others	12	6	
Unknown	15	10	
Location of TB			0.354
Peritoneum	4	18	
Bone	11	2	
Lymph node	10	4	

TB: tuberculosis; HD: hemodialysis; CAPD: continuous ambulatory peritoneal dialysis; DM: diabetes mellitus; SLE: systemic lupus erythematosus; CGN: chronic glomerulonephritis; CIN: chronic interstitial nephritis. * Values are expressed as mean±SD; # n_M:n_F=number (male):number (female)

value of 42.86 mg/dl (range from 0.5 to 202.6 mg/dl). While for ESR, 22 cases (31.43%) were reported, with a mean value 94.82 mm/h (range from 22 to 169 mm/h).

Diagnosis of TB was mainly based on the findings of positive TST, smear, culture, biopsy and polymerase chain reaction (PCR). Biopsy provided the most reliable method of diagnosis. Surgery played an important role in the process of getting a pathological examination, including laparotomy, omentectomy, parathyroidectomy, craniectomy, laminectomy, splenectomy and debridement. Positive TST, or purified protein derivative (PPD), were strong positives in four cases (Alper *et al.*, 2004; Ferrara *et al.*, 2004; Ram *et al.*, 2007; Yazici *et al.*, 2011), with a diameter of induration of 18 mm (*n*=2), 21 mm (*n*=1), and ulcerative (*n*=1). Ascite revealed the highest positive rate in the specimen of smear (33.33%, 7/21), and culture (32.14%, 9/28).

The anti-TB therapy in some cases was not clearly stated. The combined treatment of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) was the most common therapy for the extra-pulmonary TB. Less common treatments included HZE combined levofloxacin (*n*=2), HRZ combined levofloxacin (*n*=1), HRE combined streptomycin (*n*=1), and RE combined streptomycin and

moxifloxacin ($n=1$). Four cases developed obvious side effects, including hepatitis induced by PZA ($n=1$), encephalopathy caused by INH ($n=1$), peripheral neuropathy induced INH ($n=1$), behavioral abnormalities caused by INH ($n=1$). The duration of the anti-TB medication was reported for only 12 patients with a mean of 11.25 months (range from 6 to 12 months).

The majority of patients responded favorably to treatment. Twelve patients got worse, with 10 of those dying. Of the deaths, four were directly related to TB infection with three dying from TB-associated hemophagocytic syndrom (HPS) (Chien *et al.*, 2004; Ko *et al.*, 2004; Su *et al.*, 2009) and one dying from pulmonary and peritoneal TB (Gupta and Prakash, 2001). The remaining six deaths were not directly related to TB infection, including acute hypoxic respiratory failure of sepsis ($n=1$), septicemia and multiorgan failure ($n=1$), complications related to a sacral decubitus ulcer ($n=1$), bowel infarction ($n=1$), and unknown unrelated illness ($n=3$).

4 Discussion

ESRD is a well-known aggravating factor for TB infection (Yalcinkaya *et al.*, 1995; Peces *et al.*, 1996; Chou *et al.*, 2001; Summers *et al.*, 2005). Diabetes mellitus (DM), old age, male sex, malnutrition, iron overload, and dialysis inadequacy are major risk factors for TB in dialysis patients (Ahmed *et al.*, 2003; Christopoulos *et al.*, 2009; Li *et al.*, 2011). According to a report by Stevenson *et al.* (2007), patients with DM are 1.5–8.0 times more at risk to develop TB than those without DM.

The opinion was divided on the issue of catheter removal in TBP cases (Ha *et al.*, 1995; Prakash, 1999; Dervisoglu *et al.*, 2006; Borrajo Prol *et al.*, 2009). Some studies suggested the catheter be removed. Most of the cases ($n=13$) in our study had the removal of Tenckhoff catheter when TBP occurred, while some cases showed successful treatment continuing on PD ($n=5$).

There is no consensus on the optimal treatment regimen for extra-pulmonary TB in patients on dialysis (Lui *et al.*, 2001). In patients with renal failure, adjustment of doses of anti-TB drugs is required (Fang *et al.*, 1996; Fang and Huang, 1997; Lund *et al.*,

2000). In our study, the most common therapy was the quadruple treatment of HRZE, but the dose and duration in most cases were not recorded. The majority (82.86%, 58/70) made great improvements, while 10 cases died, with mortality of 14.29%.

According to previously published studies, the only statistically significant variable predisposing to a poor prognosis of TB is treatment delay (Talwani and Horvath, 2000; Ferrara *et al.*, 2004; Vadivel *et al.*, 2006). Physicians should keep diagnosis of TB in mind, especially when the clinical symptoms are non-specific and microbiological confirmation is difficult.

In conclusion, we reported four cases of extra-pulmonary TB on dialysis, and reviewed the English literature associating TB on dialysis over the last three decades. Physicians should be aware of the non-specific symptoms and location of infection, and consider TB in their differential diagnoses in dialysis patients presenting with symptoms such as fever, pain, and weight loss.

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Nkx2-1: a novel tumor biomarker of lung cancer

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Abstract: *Nkx2-1* (Nkx homeobox-1 gene), also known as *TTF-1* (thyroid transcription factor-1), is a tissue-specific transcription factor of the thyroid, lung, and ventral forebrain. While it has been shown to play a critical role in lung development and lung cancer differentiation and morphogenesis, molecular mechanisms mediating *Nkx2-1* cell- and tissue-specific expression in normal and cancerous lungs have yet to be fully elucidated. The recent identification of prognostic biomarkers in lung cancer, particularly in lung adenocarcinoma (ADC), and the different reactivity of patients to chemotherapeutic drugs have opened new avenues for evaluating patient survival and the development of novel effective therapeutic strategies. The function of *Nkx2-1* as a proto-oncogene was recently characterized and the gene is implicated as a contributory factor in lung cancer development. In this review, we summarize the role of this transcription factor in the development, diagnosis, and prognosis of lung cancer in the hope of providing insights into the utility of *Nkx2-1* as a novel biomarker of lung cancer.